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FORMULATION, DEVELOPMENT AND *IN-VITRO* EVALUATION OF DICLOFENAC TRANSDERMAL PATCHES

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Abstract:

Different polymeric Patches containing Diclofenac were prepared and evaluated for physicochemical, in vitro drug release and Kinetic studies. The IR spectral analysis of Diclofenac showed that the principal peaks and for the mixture of Diclofenac with different polymers additional to the principal peaks, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. The presence of all the characteristic bands due to functional groups in polymer mixtures suggests that there is no interaction between the drug and polymers used in the present study. Diclofenac transdermal Patches with penetration enhancers Dimethyl Sulfoxide and 15%v/w propylene glycol used as plasticizer were prepared and evaluated for physicochemical and permeation characteristics. The prepared transdermal patches were evaluated for their physiochemical characteristics such as physical appearance, weight uniformity, thickness, folding endurance; moisture content, drug content were suitable. Transdermal patches with ERS 100 and HPMC E15 showed better release than patches with ERL 100 and HPMC E15. The release rate was increased with an increase in HPMC E15 content. The release kinetics of the optimized formulations followed zero order and release mechanism was non-fickian diffusion rate-controlled mechanism. The research work gives a rational guideline for formulating a controlled release transdermal delivery system Df7 for effective therapy. The transdermal patches of Diclofenac with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

***Key Words**: Transdermal patches, Diclofenac, ERS 100, HPMC E15.*

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1. INTRODUCTION:

TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate.

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the blood stream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.[1-4]

Pathways of transdermal drug permeation[5-10]

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages (shunt routes); through the intercellular lipid domains; or by a transcellular route. A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule.

Transcellular route

Drugs entering the skin via the transcellular route pass through corneocytes. Corneocytes, containing highly hydrate keratin, provide an aqueous environment for which hydrophilic drugs can pass. The diffusion pathway for a drug via the transcellular route requires a number of partitioning and diffusion steps.

Intercellular route

The intercellular pathway involves drug diffusing through the continuous lipid matrix. This route is a significant obstacle for two reasons. (i) Recalling the 'bricks and mortar' model of the stratum corneum, the interdigitating nature of the corneocytes yields a tortuous pathway for intercellular drug permeation, which is in contrast to the relatively direct path of the transcellular route. (ii) The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into, and diffuse through repeated aqueous and lipid domains. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.

The appendageal route

Skin appendages provide a continuous channel directly across the stratum corneum barrier. However, their influence on drug penetration is hindered by a number of factors. The surface area occupied by hair follicles and sweat ducts are small (typically 0.1% of skins surface area), therefore limiting the area available for direct contact of the applied drug formulation.

2.AIM AND OBJECTIVE

AIM OF THE STUDY

The present study was designed to develop suitable matrix type transdermal drug delivery systems of Diclofenac using two different polymeric combinations, E RL100 with HPMC E 15; E RS 100 with HPMC E 15. E RL100 and E RS 100 are acrylic acid matrices which have been used to make drug-polymer matrix patches for transdermal delivery systems which are reported to be compatible with many drugs.

To prepare and evaluate Matrix type Transdermal patches of Diclofenac using two different polymeric combinations, E RL100 with HPMC E 15; E RS 100 with HPMC E 15.

OBJECTIVES OF THE WORK

- To develop the extended-release system over a period of time.
- Increased patient compliance by reducing the dose frequency
- To achieve this goal various trials are to be taken and evaluated with respect to the various quality parameters such as dissolution and related studies.
- To design customized pre-formulation studies to predict the formulation and process variables for preparation of Diclofenac transdermal patch.

PLAN OF WORK[11-13]

In order to meet the aim and objectives, the present work was planned in the following manner.

To prepare and evaluate Matrix type Transdermal patches of Diclofenac using two different polymeric combinations, E RL100 with HPMC E 15; E RS 100 with HPMC E 15.

To evaluate the dosage forms for the following:

- Weight variation
- Thickness variation
- Folding endurance
- Estimation of drug content
- Moisture content
- *In vitro* release study

3.EXPERIMENTAL METHODOLOGY[14-18]:

MATERIALS

Materials Diclofenac sodium was used as the active pharmaceutical ingredient (API), sourced from a certified supplier and tested for purity. HPMC E-15, Eudragit RS 100, Eudragit RL 100e. All materials were pharmaceutical grade.

PREFORMULATION STUDIES:

Preformulation may be described as a phase of the research & development process where the formulation scientist characterizes the physical, chemical properties of API, in order to develop stable, safe and effective dosage forms. During this evaluation possible interaction with various inert ingredients intended for use in final dosage.

Organoleptic properties:

The color, odor and taste of the drug were evaluated using descriptive terminology.

Solubility

Solubility is defined as the number of gram substance which will dissolve in 100 grams of solvent at a stated temperature. The solubility of drug was studied in different solvents such as Organic and inorganic solvents by measuring how many parts of solvent is required for one part of solid.

Melting point

Melting point of Model drug was determined by capillary method. Fine powder of Model drug was filled in glass capillary tube (previously sealed on one end). The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt. Melting point of the drug was determined by using Scientec digital melting point apparatus.

Construction of standard graph of Diclofenac

Construction of standard graph of Diclofenac in phosphate buffer pH 6.8.

The calibration curve is obtained by dissolving 50 mg of Diclofenac in 50 ml of volumetric flask and then make up with pH 6.8 phosphate buffer. From this stock-I solution 1ml solution was taken and made up to 10 ml with pH 6.8 phosphate buffer and this was stock- II. From stock-II 0.2, 0.4, 0.6, 0.8, and 1.0 ml was taken made up to 10ml with pH 6.8 phosphate buffer this gave concentration 2, 4, 6, 8and 10 µg/ml. Absorbance was measured spectrophotometrically at 272 nm against pH 6.8 phosphate buffer as blank.

Drug-Excipient Compatibility study

This was carried out by FTIR analysis of pure drug (Diclofenac), pure polymers (HPMC E 15, ERL 100 and ERS 100) and their physical mixtures as used in formulations to study the possible interaction between drug and polymers.

Preparation of Diclofenac Transdermal Patches

Matrix type transdermal patches containing Diclofenac were prepared by solvent evaporation technique, using different ratios of HPMC E 15, ERL100 (Df1 to Df4) and HPMC E 15, ERS100 (Df5 to Df8). The polymers were weighed in requisite ratios by and allowed for swelling for about 24 hrs. in solvent mixture (1:1 ratio of di-chloromethane, methanol). 15%v/w propylene glycol was incorporated as plasticizer. Then the drug solution was added to the polymeric solution, casted on to a Petri plate of surface area about 69.42sq.cm, allowed for air drying overnight followed by vacuum drying for 8-10 hr. The entire sheet was cut into 2x2 ration of small patches with an area of 6.9cm2 i.e. with a diameter of 2.9cm. About 7 patches were obtained from each sheet. All formulations carried 1ml Dimethyl Sulfoxide as penetration enhancer and Propylene glycol as plasticizer.

Table no:1. Composition of Diclofenac transdermal patches

F.Code	Drug (mg)	HPMC E15 (mg)	ERL 100 (mg)	ERS 100 (mg)	Propylene Glycol (ml)	DMSO	DCM: Methanol (1:1)	Water
DF1	126	60	160	-	5	1ml	10ml	25ml
DF2	126	120	120	-	5	1ml	10ml	25ml
DF3	126	180	80	-	5	1ml	10ml	25ml
DF4	126	240	40	-	5	1ml	10ml	25ml
DF5	126	60	-	160	5	1ml	10ml	25ml
DF6	126	120	-	120	5	1ml	10ml	25ml
DF7	126	180	-	80	5	1ml	10ml	25ml
DF8	126	240	-	40	5	1ml	10ml	25ml

Each small patch (2x2cm^2) contains 18mg of Diclofenac.
Each patch (6.9 cm^2) contains 126mg of Diclofenac

Characterization of Diclofenac Transdermal Patches [19-26]

Physicochemical properties

The Patches prepared by general procedure were evaluated for the following properties

Thickness

The thickness of the film was measured at ten different points on one film using vernier calipers. For each formulation three selected Patches were used and average thickness was recorded.

Weight variation
Eight Patches from each batch of an area of 6 cm^2 were weighed individually and the average weight was calculated.

Folding endurance
Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at the same place until broke. The number of times the strip could be folded at the same place without breaking gave the folding endurance number.

Estimation of drug content in polymeric Patches
The formulated polymeric patches were assayed for drug content in each case. Three polymeric patches from each formulation were assayed for content of drug.

Procedure
Patches from each formulation were taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 50 ml of methanol and 50 ml of dichloromethane. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 272 nm against methanol dichloromethane mixture (1:1) as blank.

Moisture Content Determination
The patches were weighed accurately and placed in a desiccator containing calcium chloride at 40°C for 24hr. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

% Moisture Content = Initial weight – Final weight/ Initial weight X 100

***In vitro* Release Franz diffusion Studies[27-30]**
The drug release studies from Diclofenac transdermal patches were performed using Franz diffusion cell. The drug containing patches was kept between donor and receptor compartments, separated from these compartments by gelatin membrane. The receptor compartment containing diffusion medium was stirred with magnetic bead operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the dialysis membrane. 3ml of sample was collected from the receptor compartment at appropriate time intervals and replaced with phosphate buffer pH 6.8. Analysis was carried out using UV-Visible spectrophotometer at 272nm against phosphate buffer pH 6.8 as reference.

Release Kinetics:
To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas model. Based on the r-value, the best-fit model was selected.

ZERO ORDER KINETICS
Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q\,t = Q\,o + K\,o\,t$$

Where Q t = amount of drug dissolved in time t.
Q o = initial amount of the drug in the solution an
K o = zero order release constant.

FIRST ORDER KINETICS
To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$Log\ Qt = log\ Qo + K1t/2.303$$

Where Qt is the amount of drug released in time t, Qo is the initial amount of drug in the solution and K1 is the first order release constant.

HIGUCHI MODEL
Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Qt = KH \cdot t1/2$$

Where Qt = amount of drug released in time t,
KH = Higuchi dissolution constant.

KORSMEYER AND PEPPAS RELEASE MODEL
To study this model the release rate data are fitted to the following equation,

$$Mt / M\infty = K \cdot t\,n$$

Where Mt / M is the fraction of drug release, K is the release constant, t is the release time and n is the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage form.

RESULT AND DISCUSSION:

PRE-FORMULATION STUDIES

Organoleptic Properties:

These test results were illustrated below:

Table no:2 Table showing the description of Diclofenac (API)

Test	Description
Colour	White to almost white crystalline powder
Odour	Free of odour

Result

The results were found as per specifications**.**

Solubility:

These tests results were illustrated below:

Table no:3 Table showing the Solubility of Diclofenac (API) in various solvents.

Solvents	Solubility
Methanol	Freely Soluble
Water	Soluble
Ethanol	Slightly Soluble

Melting Point

These tests results were illustrated below:

Table no:4 Table showing the melting point of API's

Material	Melting Point
Diclofenac	230-231 °C

Result: The Result was found to be within limit.

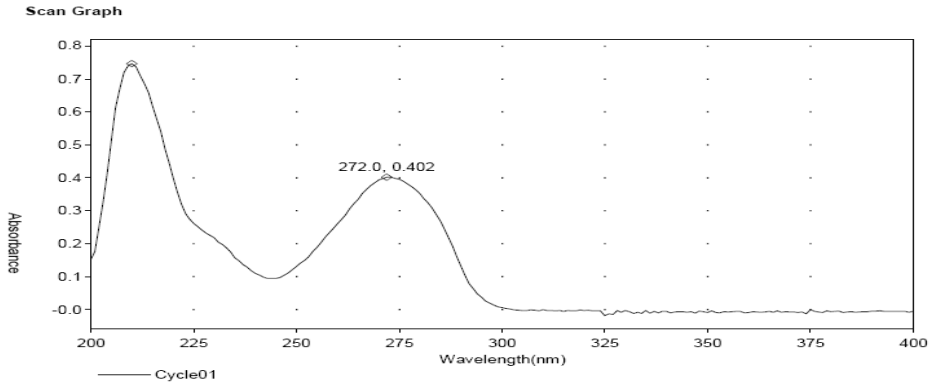

Fig no:1 UV spectrum of Diclofenac at 272nm

Construction of standard graph of Diclofenac

The standard graphs of Diclofenac in pH 6.8 phosphate buffer constructed and shown in **Fig. no.1.**The standard graphs of Diclofenac in pH 6.8 buffer have shown good linearity over a concentration range of 2 to 12µg/ml with R^2 of 0.997 respectively.

Table no:5 Standard graph of Diclofenac in pH 6.8phosphate buffer

S.No	Conc (µg/ml)	Absorbance
1	0	0
2	2	0.090
3	4	0.185
4	6	0.249
5	8	0.332
6	10	0.406
7	12	0.482

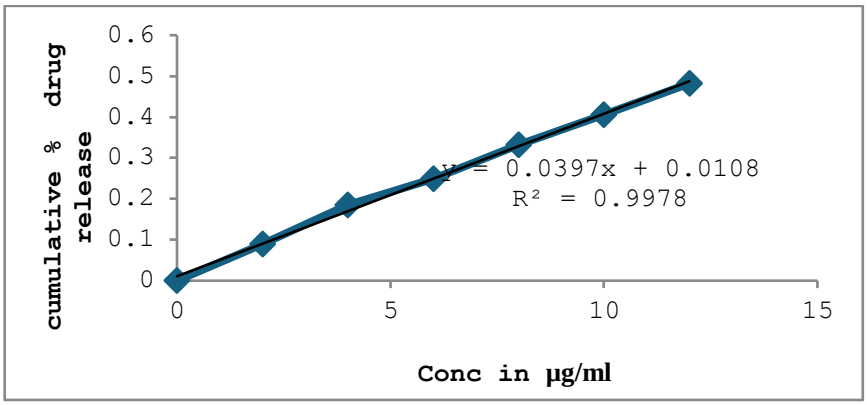

Fig 2. Standard graph of Diclofenac in pH 6.8phosphate buffer

FTIR COMPATIBILITY STUDIES:

Drug polymer compatibility studies were carried out using Fourier Transform Infra-Red spectroscopy to establish any possible interaction of Diclofenac with the polymers used in the formulation.

The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug. The results indicated that the characteristic absorption peaks due to pure Diclofenac have appeared in the transdermal patches, without any significant change in their position after successful encapsulation, indicating no chemical interaction between Diclofenac and Polymers.

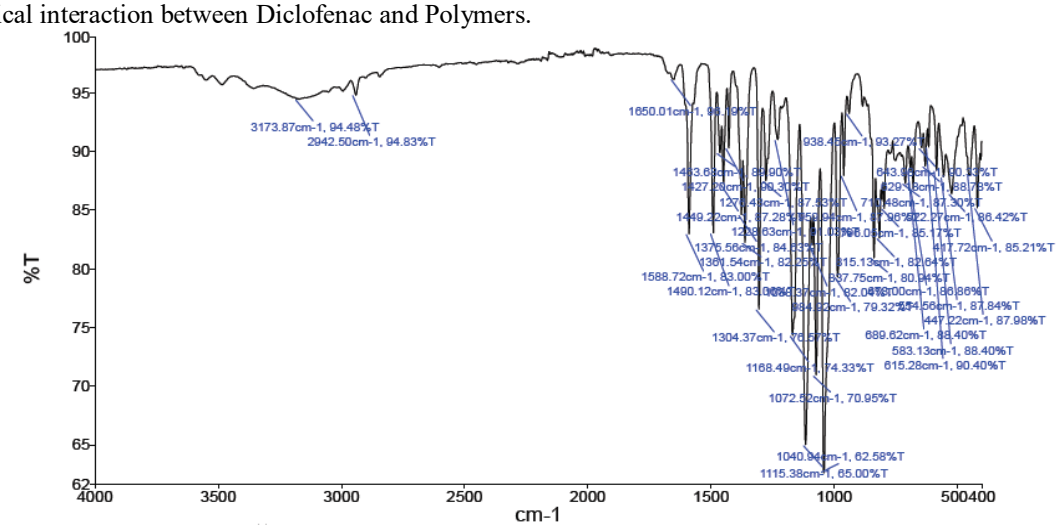

Fig.no:3 Diclofenac Pure Drug FTIR

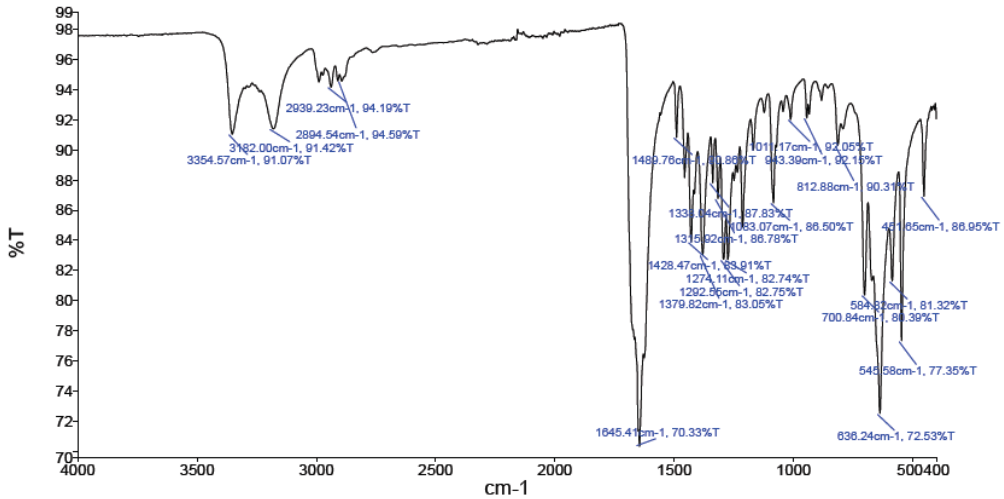

Fig.no:4 Diclofenac Final Optimized FTIR

Table no:6 FTIR Spectra of DICLOFENAC optimized

Characteristic peak	Observed range	Pure drug	Optimized formulation
O-H	3300-2500	3173.87	3182.00
N-H	3000-2800	2942.50	2939.23

FTIR Interpretation Table

FTIR studies were performed to understand the compatibilities between the drugs with different excipients. The figures above illustrate that the functional groups like O-H stretch with the observation range of 3300-2500 has peaks at 3173.87 in pure drug and 3182.00 in optimized formulation. The functional group N-H stretch has a peak range of 3000-2800 has peaks at 2942.50 in pure drug and 2939.23 in optimized formulation. The functional groups in both the pure drug and optimized formulation are found. Hence it can be concluded that the pure drug is compatible with the excipients used in the study.

Characterization of Diclofenac Transdermal Patches

1. Physicochemical properties

The Patches prepared by general procedure were evaluated for the following properties:

2. Weight Variation Test:

The results of weight variation test for various transdermal Patches were shown. Results of weight variation test indicated uniformity in weight of patches.

The weight of the patches was found to be in the range of 420mg to 432mg.

3. Thickness Variation Test:

The transdermal Patches were observed by using digital vernier caliper and found to be in the range of 0.24 mm to 0.32 mm.

4. Folding endurance number:

The folding endurance numbers of formulations are presented in the **Table. patches** did not show any cracks even after folding for more than 50 times. ERL 100 containing patches has in the range of 91 to 100, ERS 100 containing patches has in the range of 95 to 105. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing HPMC E15 content. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

5. Estimation of drug content in polymeric Patches:

The results of drug content for various transdermal Patches were shown. The results of content uniformity indicated that the drug was uniformly dispersed in all transdermal patches. The drug content analysis of the prepared formulations had shown that the process shown employed to prepare patches in the study was capable of giving patches with a uniform drug content and minimum batch variability.

6. Moisture Content study

The results of moisture content were shown in **Table**. The results revealed that the moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

Table no :7 Weight, thickness and folding endurance of Diclofenac transdermal patches

Formulation	Weight (mg)	Thickness (mm)	Folding endurance
Df1	420	0.24	91
Df2	425	0.29	92
Df3	431	0.32	94
Df4	428	0.31	100
Df5	430	0.32	95
Df6	431	0.29	97
Df7	429	0.31	105
Df8	432	0.29	99

Table no:8%Drug content and % Moisture content of Diclofenac transdermal patches

Formulation	Drug content (mg)	% Moisture content
Df1	79.7	3.8
Df2	78.5	3.5
Df3	84.8	3.6
Df4	81.1	4.2
Df5	85.5	3.9
Df6	89.4	4.1
Df7	91.1	3.5
Df8	90.3	4.4

7.%Drug content estimation:

The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability. Recovery was possible to the tune of 78.5% to 91.1%.

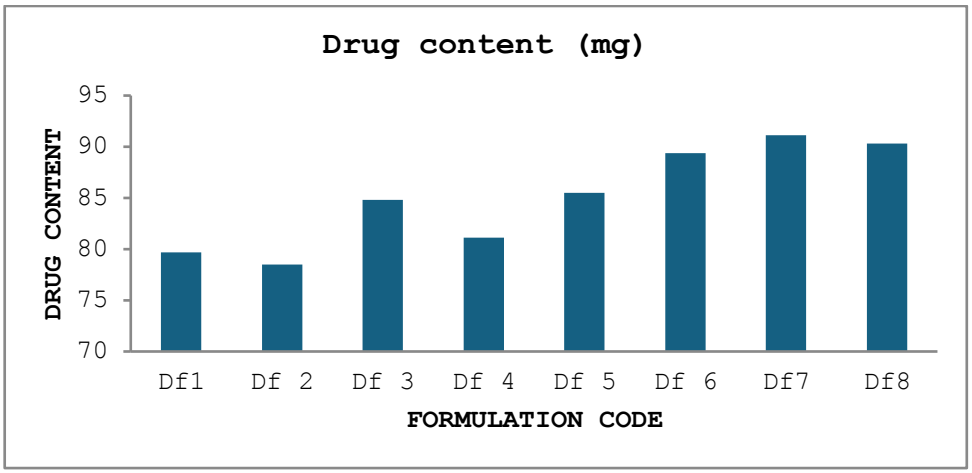

Fig.no 5: **Diclofenac transdermal patches Drug content Df1-Df8**

8. %Moisture content

The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability. Recovery was possible to the tune of 3.5% to 4.4%.

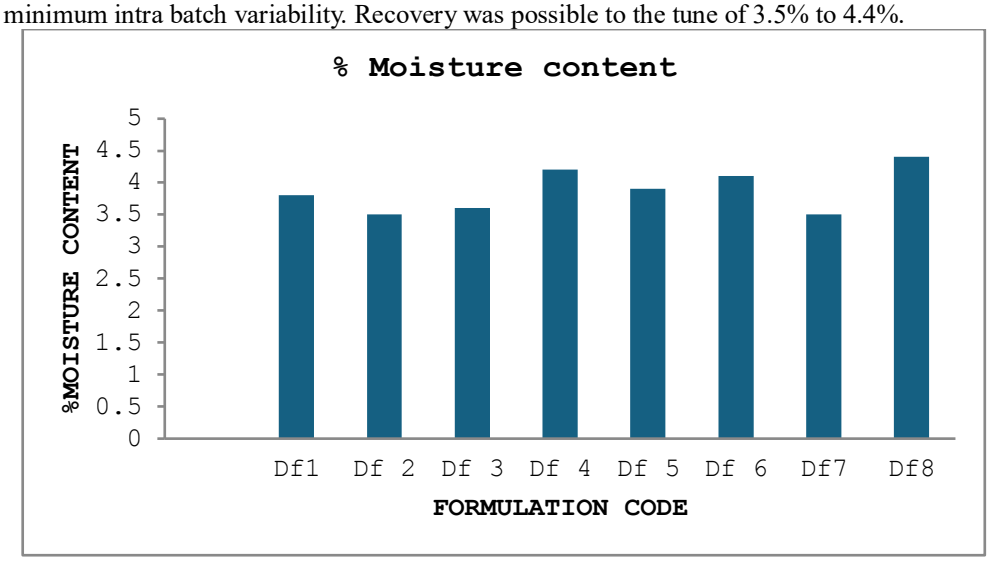

Fig.no 6: **Diclofenac transdermal patches % Moisture content Df1-Df8**

***8.Invitro* Release Studies:**

Table no. 9: Cumulative percent release of Diclofenac from transdermal patches

TIME (Hrs)	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8
0	0	0	0	0	0	0	0	0
1	10.8	9.5	6.3	22.8	17.4	17.8	14.7	17
2	36.2	16.6	24.1	35.4	32.6	34.2	27.9	22.4
3	54.3	25.7	35.4	42.8	39.8	45.9	38.6	31.3
5	67.9	37.4	46.2	55.2	48.2	59.8	50.4	45.2
8	84.4	56.2	75.3	70.1	59.4	72.16	64.8	62.2
10	95.8	75.8	94.8	92.6	64.7	82.3	78.2	72.8
12	-	89.5	-	-	72.8	91.8	98.4	92.6

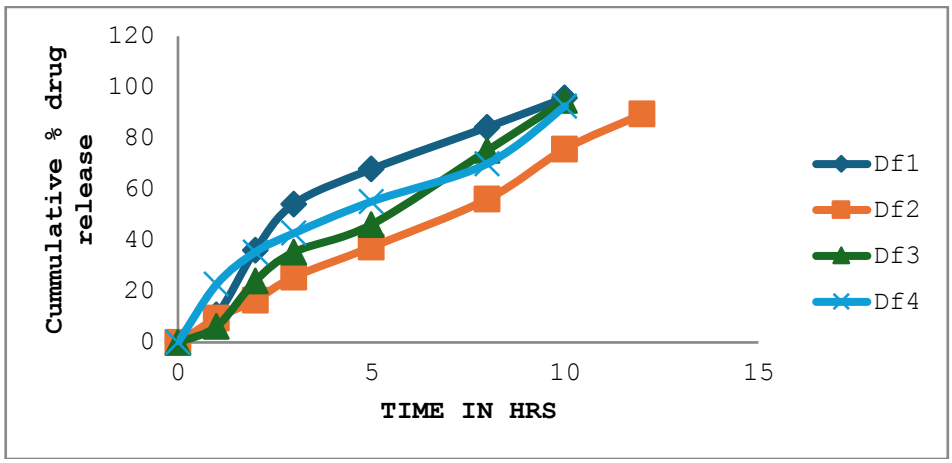

Fig.no :7 %CDR of Diclofenac from transdermal patches DF1-DF4

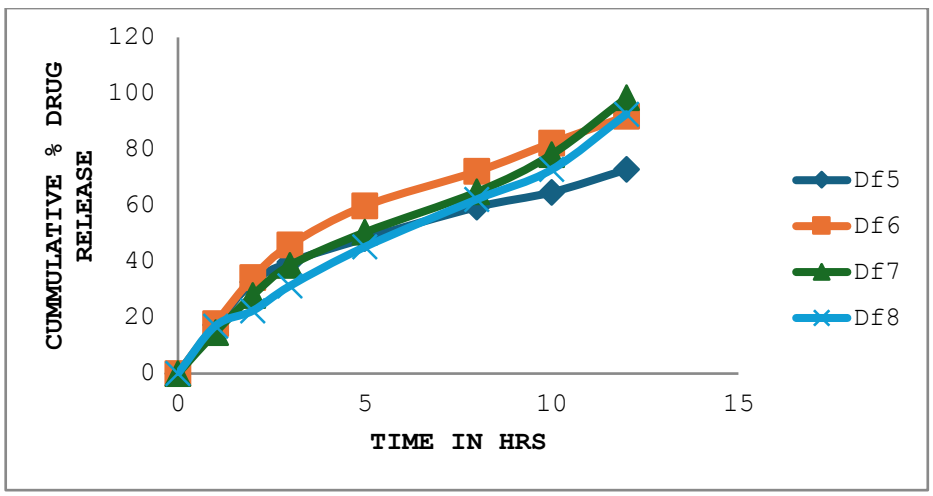

Fig.no:8 %CDR of Diclofenac from transdermal patches DF5-DF8

KINETIC STUDIES FOR OPTIMIZED Df7 FORMULATION

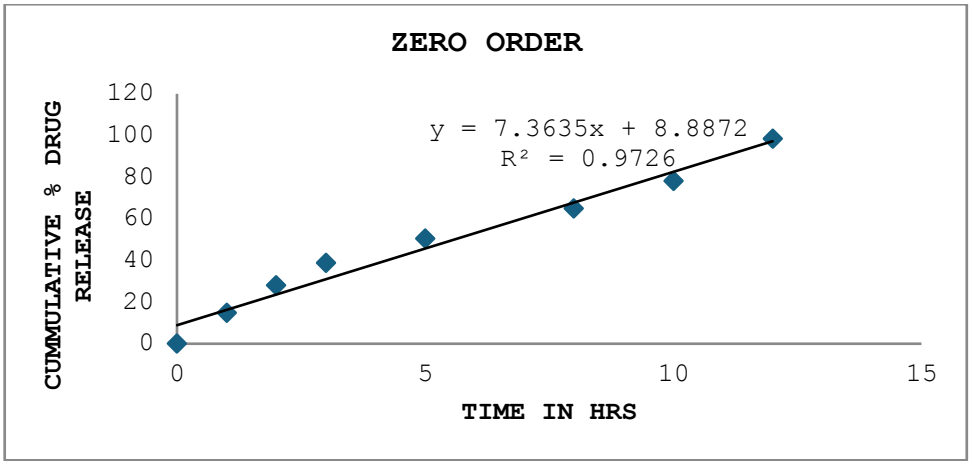

Fig.no:9 Zero order plot for optimized Df7 formulation

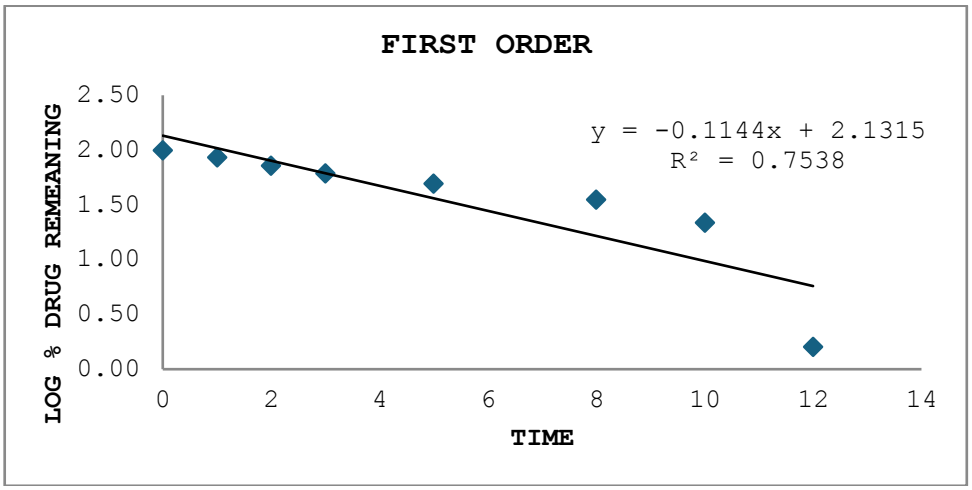

Fig.no :10 First order plot for optimized Df7 formulation

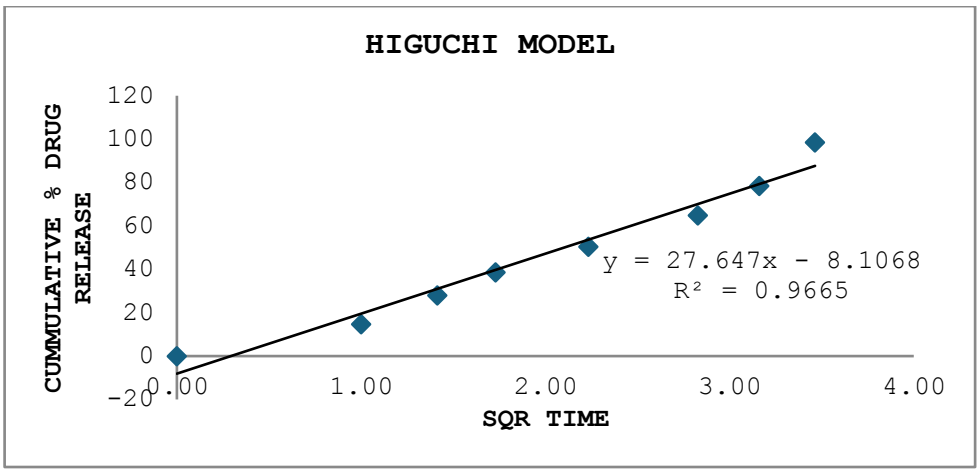

Fig.no :11 Higuchi plot for optimized Df7 formulation

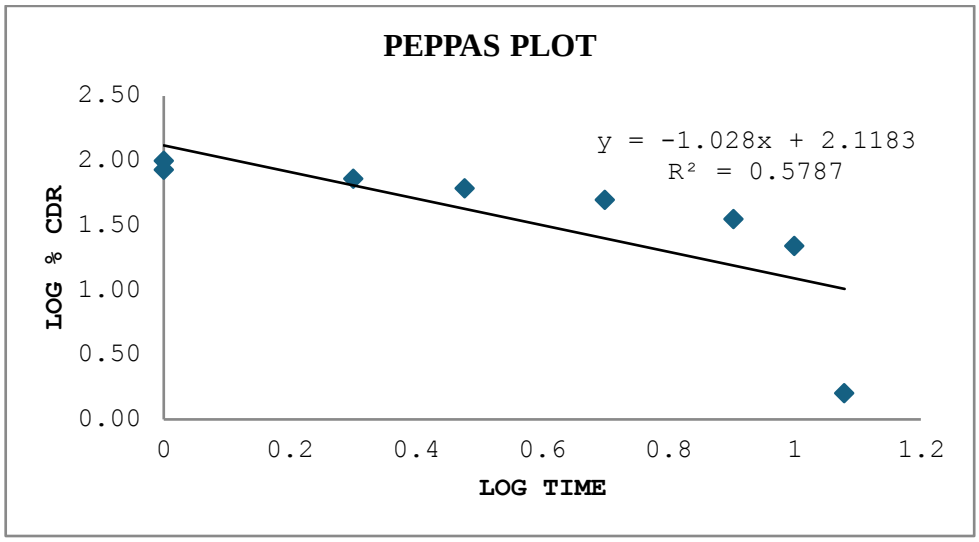

Fig.no :12 Peppas plot for optimized Df7 formulation

Table no:10 Release kinetics for optimized formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.36358904	-0.11441523	27.6477458	-1.02850711
Intercept	8.88735616	2.13195151	-8.10649194	2.11864806
Correlation	0.96980473	-0.85632620	0.96893896	0.81276379
R 2	0.97212957	0.75394563	0.96651613	0.57872931

***In vitro* Drug Release Studies from Transdermal Patches**

The cumulative amount of drug released from A and B series patches are shown in the **Tables**. 9.The results indicate that there was increase in the amount of drug release with an increase in HPMC E15.

Formulations Df7 exhibited greatest (98.4%) percentage of drug release values when compared with the other formulations. In the present study it was observed that as the concentrations of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially.

CONCLUSIONS:

Different polymeric Patches containing Diclofenac were prepared and evaluated for physicochemical, in vitro drug release and Kinetic studies.

The IR spectral analysis of Diclofenac showed that the principal peaks and for the mixture of Diclofenac with different polymers additional to the principal peaks, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. The presence of all the characteristic bands due to functional groups in polymer mixtures suggests that there is no interaction between the drug and polymers used in the present study.

Diclofenac transdermal Patches with penetration enhancers Dimethyl Sulfoxide and 15%v/w propylene glycol used as plasticizer were prepared and evaluated for physicochemical and permeation characteristics.

The prepared transdermal patches were evaluated for their physiochemical characteristics such as physical appearance, weight uniformity, thickness, folding endurance; moisture content, drug content were suitable.

Transdermal patches with ERS 100 and HPMC E15 showed better release than patches with ERL 100 and HPMC E15. The release rate was increased with an increase in HPMC E15 content.

The release kinetics of the optimized formulations followed zero order and release mechanism was non-fickian diffusion rate-controlled mechanism.
The research work gives a rational guideline for formulating a controlled release transdermal delivery system Df7 for effective therapy.

The transdermal patches of Diclofenac with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

REFERENCES:

1. Ansel, Pharmaceutical Dosage form and Drug Delivery System, Lippincott, 7th edition: 553.
2. Gennaro R.A. Remington, The Science and Practice of Pharmacy., 20th ed. New york: Lippincott Williams: (2000) ,1045.
3. Chien Yie W., Transdermal Therapeutic systems, Controlled Drug Delivery: Fundamentals & Applications. Robinson Joseph R, LeeVincent HL. eds, New York: Marcel Dekker (1987), 523.
4. B.S. Dave et al., Studies on effect of Limonene and other formulation ingredients on permeation of Diclofenac sodium through rat skin, International Journal of Pharmaceutical Excipients, 2(2), (2003), 50-54.
5. Jitendra Banweer et al., Formulation, Optimization and Evaluation of Matrix type Transdermal system of Lisinopril Dihydrate Using Permeation Enhancers, Drug Invention Today, 2(2), (2010) , 134-137.
6. A. Bhattacharya et al., Effect of hydrophobic permeation enhancers on the release and skin permeation kinetics from matrix type transdermal drug delivery system of ketotifen fumerate, Acta Poloniac Pharmaceutica-Drug Research, 58(2), (2001), 101-105.
7. Naohiro Nishida et al., Development and evaluation of a monolithic drug in adhesive patch for valsartan, International Journal of Pharmaceutics, 402, (2010), 103- 109.
8. Chien Yie W. Transdermal Therapeutic systems, Conrolled Drug Delivery: Fundamentals & Applications. Robinson Joseph R, LeeVincent HL. eds, New York: Marcel Dekker (1987), 523.
9. Divyesh patel et al., Transdermal drug delivery system: Review, International Journal of Biopharmaceutical and Toxicological Research, 1(1), (2011), 61-80.
10. N. S Chandrashekar et al., Physicochemical and Pharmacokinetic parametres in drug selection and loading for Transdermal drug delivery, Indian Journal of Pharmaceutical Sciences, (2008), 70.
11. Chien Yie W. In Transdermal Drug Delivery & Delivery Systems, Novel drug Delivery Systems. eds, New York: Marcel Dekker (1992), 301.
12. S.P. Vyas and Khar, Control Drug Delivery Concepts and Advances, 411-447.
13. Snigdha Bharadwaj et al., Recent advancement in transdermal drug delivery system, International Journal of Pharma Professsional's Research, 2(1), (2011).
14. J. Ashok kumar et al., Transdermal drug delivery system: An Overview, International Journal of Pharmaceutical Sciences Review and Research, 3(2), (2010), 49-54.
15. Santosh Kumar, Ajay Kumar Chaudhary, Prithvi Kumar Singh, Reetu Verma, Girish Chandra, Vinod Kumar Bhatia, Dinesh Singh, and Jaishri BograTransdermal Buprenorphine Patches for Postoperative Pain Control in Abdominal Surgery Buprenorphine is a semi-synthetic derivative of the baine; its low concentration is sufficient to provide effective pain relief.
16. R. Panner Selvam et al., Transdermal drug delivery systems for antihypertensive drugs, International Journal of Pharmaceutical and Biomedical Research 01(01), (2010).
17. Jitendra Banweer et al., Formulation, Optimization and Evaluation of Matrix type Transdermal system of Lisinopril Dihydrate Using Permeation Enhancers, Drug Invention Today 2(2), (2010), 134-137.
18. J. R. D Gupta et al., Formulation and Evaluation of Matrix type Transdermal patches of glibenclamide.,International Journal of Pharm sciences and Drug research.,2009.,1(1):46-50.
19. Mamatha T et al., Transdermal Drug Delivery System for Atomoxetine Hydrochloride – In vitro and Ex vivo Evaluation, Current Trends in Biotechnology and Pharmacy, Volume 3 (2) April – 2009.
20. Anil J Shinde et al., Development and characterization of transdermal therapeutics system of tramadol hydrochloride, Asian J Pharm 2008;2:265-9.
21. Ramesh Gannuet al.,Development of Nitrendipine Transdermal Patches:*Invitro* and *Ex vivo* Characterization, Current DrugDelivery, 4, (2007),69-76.
22. Gattani S.G et al., Formulation and evaluation of Transdermal films of Ondansetron Hydrochloride, Indian Drugs, 43(3), (2006), 245-250.
23. Sadhana P. Guptha et al., Effective and controlled transdermal delivery of Metaprolol Tartrate, Indian Journal of Pharmaceutical Sciences , 67(3), (2005) ,346-350.
24. M. Aqil et al.,*In vivo* Characterization of Monolithic Matrix Type Transdermal Drug Delivery Systems of Pinacidil Monohydrate: A Technical Note, AAPS Pharm SciTech, (2005),1-10.
25. B.S. Dave et al., Studies on effect of Limonene and other formulation ingredients on permeation of Diclofenac sodium through rat skin, International Journal of Pharmaceutical Excipients, 2(2),(2003), 50-54.

26. Amit Kumar Jain et.al., Reported effects of terpenes on transdermal delivery of imipramine hydrochloride (2002) Feb 19;79(1-3):93-101.
27. A. Bhattacharya et al., Effect of hydrophobic permeation enhancers on the release and skin permeation kinetics from matrix type transdermal drug delivery system of ketotifen fumerate, Acta Poloniac Pharmaceutica-Drug Research 58(2), (2001), 101
28. http://www.drugbank.com
29. Mandal S. C et al., In vitro release and permeation kinetics of pentazocine from matrix-dispersion type transdermal drug delivery systems, Drug Development and Industrial Pharmacy 20(11), (1994), 1933-1941.
30. Rao PR, Reddy MN. Comparative in-vivo evaluation of propranolol hydrochloride after oral and transdermal administration in rabbits. Eur J Pharm Biopharm 2003;56(1):81-5.